DRUG NAME: Cladribine

SYNONYM(S): CdA,[1] 2-CdA,[1] 2-chloro-2'-deoxyadenosine[2]

COMMON TRADE NAME(S): LEUSTATIN®

CLASSIFICATION: antimetabolite, cytotoxic[3]

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Like fludarabine, cladribine is a synthetic purine nucleoside prodrug that is resistant to deamination by adenosine deaminase which permits intracellular accumulation.[1] Cladribine is phosphorylated via deoxycytidine kinase to the active triphosphate derivative (CdATP) which inhibits ribonucleotide reductase.[4] In cells such as lymphocytes with high levels of deoxycytidine kinase and low levels of deoxynucleotidase, CdATP also prevents elongation of DNA strands via direct incorporation into DNA as a false nucleotide.[1,4] Depletion of adenine dinucleotide and adenosine triphosphate (ATP) also occurs.[1,4] Unlike other drugs that affect purine metabolism, cladribine has cytotoxic effects on actively dividing and resting cells.[4] Cladribine is an immunosuppressive agent.[4]

PHARMACOKINETICS:

Oral Absorption	oral solution: 37-55%[5,6]; investigational	
Distribution	extensive[2]	
	cross blood brain barrier?	yes; ~25% of plasma concentration
	volume of distribution (V_D)	4.52 $\pm$ 2.82 L/kg
	plasma protein binding	20%
Metabolism	phosphorylated to CdATP	
	active metabolite(s)	CdATP
	inactive metabolite(s) [5]	chloroadenine
Excretion	biphasic	
	urine[4,6]	18-44%
	feces	no information found
	terminal half life	5.4 h
	clearance	664 ml/h/kg 29.5 $\pm$ 8.3 L/h/m^2
Children[7,8]	V_D=305-357 L/m^2; clearance=39 L/h/m^2; longer terminal half life than adults	

Adapted from standard reference[4] unless specified otherwise.

USES:

Primary uses:
*Leukemia, hairy cell

Other uses:
Leukemia, chronic lymphocytic[1,6]
Leukemia, chronic myelogenous[6]
Lymphoma, cutaneous T-cell[1]
Lymphoma, non-Hodgkin's[1,6]

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Cladribine produces ***severe myelosuppression***; monitor hematologic function regularly especially during the first 4-8 weeks after therapy.[4]

High-doses (4-9 times the recommended dose for hairy cell leukemia) as preparation for BMT, have been associated with:

- serious neurotoxicity including irreversible paraparesis and quadriparesis (35-45%)[1,4]
- acute nephrotoxicity (19-45%)[1,4]
- severe bone marrow suppression[4]

Hepatitis B (HBV) reactivation: All lymphoma patients should be tested for both HBsAg and HBcAb. If either test is positive, such patients should be treated with lamivudine 100 mg/day orally, for the entire duration of chemotherapy and for six months afterwards. Such patients should also be monitored with frequent liver function tests and HBV DNA at least every two months. If the HBV DNA level rises during this monitoring, management should be reviewed with a hepatologist and consideration given to halting chemotherapy.[9,10]

Carcinogenicity: not studied to date[4]; based on genotoxicity, carcinogenicity cannot be ruled out [4]

Mutagenicity: Not mutagenic in Ames test and mammalian *in vitro* mutation test.[4] Cladribine is clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.[4]

Fertility: effect unknown[4]; in monkeys, cladribine affects testicular cells[4]

Pregnancy: FDA Pregnancy Category D.[6] Although there is no evidence of teratogenicity in humans, teratogenic effects and fetal mortality have been observed in animals[6]; other drugs that inhibit DNA synthesis have been reported to be teratogenic.[4]

Breastfeeding is not recommended due to the potential secretion into breast milk.[4]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.[9]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics*** ***At recommended doses, most nonhematologic adverse effects are typically mild to moderate in severity.***[1]	
blood/bone marrow/ febrile neutropenia	anemia (severe 37%) nadir typically occurs during the first 2 weeks with recovery by week 8; hemolytic anemia and aplastic anemia also reported
	bone marrow hypocellularity (34%); prolonged hypocellularity (32 months) has been reported
	erythroid macrocytosis[1]; prolonged, reported in patients who received up to 6 courses of cladribine[1]
	lymphopenia; may be significant and prolonged ***neutropenia*** (severe 70%); nadir typically occurs during the first 2 weeks with recovery by week 5 ***febrile neutropenia*** (47%) 32% with severe neutropenia hypereosinophilia; typically occurs in patients receiving multiple courses of cladribine[1]
	myelosuppression; dose-related, most notable during the first month after treatment
	thrombocytopenia (12%); nadir typically occurs during the first 2 weeks with recovery by day 12; recovery may be delayed in patients with severe baseline thrombocytopenia[1]
cardiovascular (arrhythmia)	tachycardia ($\leq$6%)[1,4,6]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
At recommended doses, most nonhematologic adverse effects are typically mild to moderate in severity.[1]	
constitutional symptoms	chills (≤9%)[1,4,6]
	fatigue (≤45%), asthenia (≤9%)[1,4]
	fever (67-69%, severe 11%); during the first month of therapy; less than 1/3 of febrile events are associated with a documented infection
	insomnia (≤7%)[1,4]
	diaphoresis (≤9%)[1,4,6]
dermatology/skin	*extravasation hazard: none*[11]
	injection site reaction (≤19%); including redness (≤6%),[1,4] swelling, pruritis (≤6%),[1,4] pain (≤6%)[4]
	phlebitis (2%); likely related to the infusion procedure and/or indwelling catheter rather than the treatment
	rash (≤27%); typically mild
	Stevens-Johnson syndrome and toxic epidermal necrolysis (<1%)
	urticaria; typically occurs in patients receiving multiple courses of cladribine[1]
gastrointestinal	*emetogenic potential: rare*[12]
	anorexia (≤17%)[1,4]
	constipation (≤9%)[1,4,6]
	diarrhea (≤10%)[1,4,6]
	nausea (28%); typically mild and not associated with vomiting
	vomiting (≤13%)[1,4,6]
hemorrhage	epistaxis (>5%)[1,4,6]
	purpura (≤10%),[1,4,6] petechiae (≤8%)[1,4,6]
hepatobiliary/pancreas	elevated bilirubin and transaminases; reversible and typically mild; typically occurs in patients receiving multiple courses of therapy[1]
infection	***immunosuppression***; prolonged depression of CD4 counts and transient suppression of CD8 counts; CD4 nadir typically occurs during the first 4-6 months with recovery by 40 months; prolonged lymphopenia has occurred
	infection (28%); during the first month after treatment; including serious infection e.g., septicemia, pneumonia (6%) and those associated with immunosuppression e.g., opportunistic infections: fungal, viral; deaths have occurred
lymphatics	edema (≤6%)[1,4,6]
metabolic/laboratory	hyperuricemia
musculoskeletal	myalgia (≤7%)[1,4,6]; arthralgia (>5%)[1,4,6]
	weakness (9%)[6]
neurology	dizziness (≤9%)[1,4,6]
	neurotoxicity (severe <1%); with standard-dose neurotoxicity (35-45%)[1,4]; with high-dose (4-9 times the recommended dose); may be severe and irreversible including peripheral polyneuropathy, paraparesis, and quadriparesis

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics*** ***At recommended doses, most nonhematologic adverse effects are typically mild to moderate in severity.***[1]	
pain	abdominal pain (≤6%)[1,4,6]
	headache (≤22%)
	trunk pain (≤6%)[1,4]
pulmonary	abnormal breath sounds (≤11%)[1,4,6]
	cough (≤10%)[1,4,6]
	dyspnea (≤7%)[1,4,6]
	pulmonary interstitial infiltrates; typically of infectious etiology
renal/genitourinary	renal insufficiency (19-45%)[1,4]; with high-dose (4-9 times the recommended dose); not reported with standard doses
secondary malignancy	myelodysplastic syndrome (0.03%)
syndromes	tumour lysis syndrome (<1%)
vascular	thrombosis (2%); likely related to the infusion procedure and/or indwelling catheter rather than treatment

Adapted from standard reference[4] unless specified otherwise.

Hyperuricemia may result from cell lysis by cytotoxic chemotherapy and may lead to electrolyte disturbances or acute renal failure.[13] It is most likely with highly proliferative tumours of massive burden, such as leukemias, high-grade lymphomas, and myeloproliferative diseases. The risk may be increased in patients with preexisting renal dysfunction, especially ureteral obstruction. Suggested prophylactic treatment for high-risk patients[14]:

- aggressive hydration: 3 L/m^2/24 hr with target urine output > 100 mL/hr
- if possible, discontinuation of drugs that cause hyperuricemia (e.g., thiazide diuretics) or acidic urine (e.g., salicylates)
- monitoring of electrolytes, calcium, phosphate, renal function, LDH, and uric acid q6h x 24-48 hours
- electrolyte replacement as required
- allopurinol 600 mg po initially, then 300 mg po q6h x 6 doses, then 300 mg po daily x 5-7 days

Urine should be alkalinized only if the uric acid level is elevated, using sodium bicarbonate IV or PO titrated to maintain urine pH > 7. Rasburicase (FASTURTEC®) is a novel uricolytic agent that catalyzes the oxidation of uric acid to a water-soluble metabolite, removing the need for alkalinization of the urine.[15] It may be used for treatment or prophylaxis of hyperuricemia, 0.2 mg/kg IV daily for up to 7 days; however, its place in therapy has not yet been established.

INTERACTIONS: no documented interactions

SUPPLY AND STORAGE:

Injection[4]: Janssen-Ortho Inc. supplies cladribine as a preservative-free 10 mg/10 mL solution. Store in the refrigerator, protect from light during storage. Freezing does not affect the solution. If freezing occurs, thaw at room temperature, do not refreeze.

For basic information on the current brand used at the BC Cancer Agency, see Chemotherapy Preparation and Stability Chart in Appendix.

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at the BC Cancer Agency, see Chemotherapy Preparation and Stability Chart in Appendix.

Additional information: must be diluted prior to intravenous administration[4]

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

BCCA administration guideline noted in ***bold***, ***italics***

Subcutaneous[2,6,10]	***rotate sites on thighs, abdomen, and flank***
Intramuscular	no information found
Direct intravenous[4]	not recommended; must be diluted prior to intravenous administration[4]
Intermittent infusion[4,6]	***over*** 1-***2 h***
Continuous infusion[4]	***over 24 h; 7-day infusions have been used***
Intraperitoneal	no information found
Intrapleural	no information found
Intrathecal	no information found
Intra-arterial	no information found
Intravesical	no information found

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

***Adults*:**

BCCA usual dose noted in ***bold, italics***

	Cycle Length:	
Intravenous:	n/a[6,10]:	***0.14 mg/kg*** *(*range 0.028-0.14 mg/kg) ***IV or SC once daily for 5 consecutive days starting on day 1*** (total dose 0.7 mg/kg [range 0.14-0.7 mg/kg])
	n/a[41,6]:	0.09-0.1 mg/kg IV over 24 hours for 7 consecutive days starting on day 1 (total dose 0.63-0.7 mg/kg) • may be administered as a continuous 7-day infusion
	n/a[2,4]:	3.6 mg/m^2 IV over 24 hours for 7 consecutive days starting on day 1 (total dose 25.2 mg/m^2) • may be administered as a continuous 7-day infusion

BCCA usual dose noted in ***bold, italics***

Cycle Length:
n/a[1,6]: 3.4 mg/m^2 SC once daily for 7 consecutive days starting on day 1
(total dose 23.8 mg/m^2)

Concurrent radiation: no information found

Dosage in myelosuppression: modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix 6 "Dosage Modification for Myelosuppression"

Dosage in renal failure: use with caution[4]; dosage adjustment recommendations exist[16], including the following [10]:

Creatinine clearance (mL/min)	Dose
>70	100%
30-70	60%
<30	do not use

Calculated creatinine clearance = $\frac{N^* \times (140 - Age) \times weight\ in\ kg}{Serum\ Creatinine\ in\ \mu mol/L}$

* For males N=1.23; for females N=1.04

Dosage in hepatic failure: use with caution[4]

Dosage in dialysis: unknown if removed by dialysis[1]

Children:

safety and effectiveness have not been established[4]; has been used[1,6-8]

*Cladribine IV solutions prepared with bacteriostatic NS, for a 7-day infusion, contain benzyl alcohol and should NOT be used in neonates[4]

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